Accessing Polyoxygenated Dibenzofurans via the Union of Phenols and o-Benzoquinones: Rapid Syntheses of Metabolites Isolated from Ribes takare

Meng Yao Zhang and Russell A. Barrow*

Research School of Chemistry, Australian National University, Acton, ACT 2601, Australia

Supporting Information

ABSTRACT: The construction of polyoxygenated dibenzo-[b,d]furan frameworks from the union of substituted phenols/naphthols and o-benzoquinones via a Michael-oxidation-oxa-Michael cascade is reported. The power of this transformation is demonstrated in the generation of a library of highly substituted dibenzofurans, featuring specifically substituted molecules containing broad ranges of functionality. The utility of this method is showcased in the total syntheses of two dibenzofurans isolated from Ribes takare, assembling the carbon scaffold of both natural products in one operation.

Oxygen-rich dibenzofurans are a class of compounds prevalent in nature.1 Their unique structural features and promising biological activity have continuously inspired the synthetic community toward development of methodologies that have allowed for the preparation of a diverse array of natural/unnatural products bearing this structural motif.2 Cycloeulecomelone (1),3 vialinin B (2),4 boletopsin 13 (3),5 and popolohuanone E (4)6 are examples of bioactive natural products containing the dibenzofuran/dibenzofuranquinone substructure. Recently, two novel dibenzofurans 5 and 6 possessing α-glucosidase inhibitory activity were isolated from the aerial parts of Ribes takare D. Don by Chen et al. (Figure 1).7

Unsurprisingly, the most challenging part of the synthesis of polyoxygenated dibenzofurans is the construction of the densely substituted dibenzofuran core. Previous synthetic routes toward functionalized dibenzofurans have traversed oxidative couplings and intramolecular nucleophilic substitution of hydroxylated biphenyl frameworks (or their oxidized quinone forms).2a,8 The Anderson group presented a base catalyzed intramolecular condensation toward the construction of the dibenzofuranquinone core in their biomimetic study of popolohuanone E (Scheme 1, eq 1).6 In the synthesis of vialinin B reported by Ye and co-workers, the dibenzofuran core of the natural product was accessed via copper(1)

Scheme 1. Syntheses of Polyoxygenated Dibenzofurans

Figure 1. Dibenzofuran natural products.

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mediated Ullmann coupling (Scheme 1, eq 2). Pan and co-workers disclosed a silver(I) oxidation followed by an intramolecular oxa-Michael addition of the hydroxyl moiety to the o-benzoquinone in their syntheses of anastatins A and B (Scheme 1, eq 3).

We were interested in developing a complementary approach that would permit access to the dibenzofuran framework directly from unprotected phenols and o-benzoquinones, rather than from biphenyl precursors. Nevertheless, promising results have been reported that exploit o-benzoquinones as powerful building blocks to rapidly access complex targets, such as various coumarins and bipleiophylline.11 With the right conditions, we envisioned that the dibenzofuran framework could be accessed via the union of phenols and o-benzoquinones in a single operation through a formal (3 + 2) cycloaddition or Michael-oxidation-oxa-Michael type process.

The dibenzofuran synthesis was first investigated using sesamol (7a) as the phenolic component, o-benzoquinone (8), and MeMgCl as the base, as outlined in Table 1. Dibenzofuran formation was observed when the reaction temperature was lowered (entry 2). Isolated yields increased when the reaction temperature was maintained and quenched at −78 °C (entry 3). Furthermore, the yield of 10a increased when the reaction temperature was maintained and quenched at −78 °C (entry 4). Increasing the number of equivalents of o-benzoquinone enhanced the consumption of sesamol, and ultimately the yield as determined by NMR was improved to 43% (entry 7).

Purification of the dibenzofurans presented a considerable challenge due to the highly polar nature of the catechol functionality, and use of conventional silica gel chromatography consistently resulted in 20–25% loss of product. Among other types of chromatographic supports used, including alumina and reverse phase silica, gel permeation chromatography using Sephadex LH-20 was found to be the most effective, affording dibenzofuran 9a in 40% isolated yield.

With the optimized conditions (Table 1, entry 7) in hand, the scope of this presumed Michael-oxidation-oxa-Michael cascade was explored with a diverse collection of phenols. Initially, the reactivity of various 4-substituted sesamol coupling partners was investigated. The transformation was tolerant of functionalities extending from bromide, benzyl, and prenyl groups, affording the desired dibenzofurans in moderate yields (Scheme 2, 9b, 9c, and 9d). Similarly, 2,3,4-trimethoxyphenol reacted with o-benzoquinone to give the desired trimethoxy-
dibenzofuran catechol 9e in 26% yield. A diminished yield was observed with 3-methoxy-4-(4-methoxyphenyl)phenol (9f), and dibenzofuran formation was not observed with 4-methoxy, 3-methoxy, 3,4-dimethyl, or 3-chloro-4-methoxyphenol (7g, 7h, 7i, 7j). The outcomes suggest that the presence of strongly electron-donating groups (EDGs) on the 3,4-positions of the phenolic coupling partner are crucial for successful dibenzofuran formation.

While competing reactivity of the nucleophile involved in the initial Michael reaction had been detected previously (Table 1, entries 3 and 4), we observed exclusive reactivity through C-4 when 3,4,5-trimethoxyphenol or 3-methoxy-1-naphthol were subjected to the reaction conditions, producing compounds 10k and 10l respectively (Scheme 2). This was remarkable in the case of 10k, favoring the formation of the de aromatized cyclohexa-2,5-dien-1- one, indicating a clear preference for addition at the para carbon in substrates of this nature. We have also recognized the potential for the reaction to be applied in the generation of oxygenated biphenyl compounds such as 10l.

The formal (3 + 2) cycloadditions of 1-naphthols with o-benzoquinone were also examined. Subjecting a range of 1-naphthols that contain EDGs at the 4-position (methoxy, 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 2-furanyl) to the optimized reaction conditions furnished the desired dibenzofurans 9m, 9n, 9o, and 9p in slightly higher yields compared to the phenolic coupling counterparts (Scheme 2). However, the annulation of 4-bromo-1-naphthol (7q) could not be achieved, reinforcing the necessity of the EDG at the 4-position which presumably enhances the nucleophilicity of the phenolate. The union of 2-naphthol 7r and o-benzoquinone was also unsuccessful. We anticipate this procedure, effectively forming two bonds and a ring in a single operation, will find wide application and entry into uncharted dibenzofuran chemical space via simple modifications of phenols.

The synthetic utility of this methodology was further highlighted through the first syntheses of the dibenzofuran-containing natural products 5 and 6. As depicted in Scheme 3, 4-methoxydibenzo[ff]furan catechols 11 and 12 were constructed in 41% (56% BRSM) and 38% (61% BRSM) yields respectively, from common quinone 13, and phenolates 14 and 15. Not only does this reaction forge the entire carbon skeleton of the natural product in a single operation, it demonstrates the fact that our annulation protocol is tolerant of functionalized o-benzoquinones in addition to the parent compound. In addition, the regioselective nature of the first 1,4-addition at the o-benzoquinone 13 was recognized, resulting in the formation of 4-methoxydibenzo[ff]furans 11 and 12 exclusively. The regioslectivity of this transformation could be explained by the preferential Michael addition at the more electrophilic C-5 of quinone 13.

Alkylation of the catechol moiety using dibromomethane and cesium carbonate produced the trimethoxy natural product 5. The Michael adduct 17 was isolated in 23% yield (Scheme 3) supporting a putative mechanism whereby the Michael addition occurs first, forming the C-C biphenyl linkage. The intermediacy of the biphenyl compound 17 was then examined by subjecting it to the reaction conditions. A solution of 17 in THF at 0 °C, under an argon atmosphere, was treated with MeMgCl (1.1 equiv) followed by cooling the reaction mixture to −40 °C. Unsurprisingly, dibenzofuran 11 was not observed in the reaction mixture at this stage. However, after addition of 1.2 equiv of o-benzoquinone 13, approximately 80% conversion to 11 was observed. These observations support the dual role of the o-benzoquinone as both the Michael acceptor and oxidant in the reaction. We propose the mechanism proceeds through oxidation of the catecholate monoanion in the intermediate following the initial Michael addition generating an o-quinone that acts as the oxa-Michael acceptor in the subsequent reaction in the cascade.

In summary, a new method for the rapid construction of polyoxygenated dibenzo[h,d]furan scaffolds has been developed. The procedure involves the annulation of readily available phenols/naphthols with o-benzoquinones which concisely orchestrates a Michael-oxidation-oxa-Michael sequence in a single operation. Successful application of this method enabled the first divergent syntheses of two dibenzofuran natural products 5 and 6 in three and five steps, respectively. Given the prevalence of oxygen-rich dibenzofurans in nature, we envision that this approach holds great potential to broaden the accessibility to a diverse

**Scheme 3. Application in Total Syntheses of Dibenzofuran Natural Products 5 and 6 Isolated from Ribes takare**

![Scheme 3 Diagram](Image)

“Dibenzofuran formation: Reactions were performed with phenol (1.0 equiv), MeMgCl (1.3 equiv), and 3-methoxy-o-benzoquinone (1.2 equiv) in 20 mL of THF unless otherwise noted. Isolated yields unless otherwise noted. °BRSM yields. Reaction was performed with phenol (1.0 equiv), MeMgCl (1.1 equiv), and 3-methoxy-o-benzoquinone (1.2 equiv) in 20 mL of THF.”

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collection of dibenzofuran-containing natural/unnatural compounds.

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